

Allergy to sulfonamides

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List of Design Committee Members: Benno Schnyder, MD, and Werner J. Pichler, MD (authors), and James T. Li, MD, PhD (series editor)

Activity Objectives

1. To recognize the various clinical pictures of allergic reactions to sulfanilamides.
2. To understand the possible immune mechanism to sulfonamides, particularly sulfanilamides.
3. To understand the cross-reactivity or lack of it between sulfonamide-containing drugs.
4. To know the clinical characteristics and variable clinical course of drug rash with eosinophilia and systemic symptoms (DRESS; or D[i]HS).

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CLINICAL VIGNETTE

A 48-year-old man was referred to our clinic with high-grade intermittent fever for 8 days and a generalized rash for 3 days. Three weeks before presentation, the patient had been started on 5 mg/d prednisolone, 50 mg of diclofenac twice daily, 20 mg/d omeprazole, and 2 g/d of sulfasalazine for symptomatic ankylosing spondylitis. During the initial evaluation, he was febrile (39.7°C), had bilateral inguinal lymph node enlargements, and had a diffuse erythematous exanthema (see Fig E1 in this article's Online Repository at www.jacionline.org) without blistering. His face was swollen, but he had no mucosal involvement or conjunctivitis. He had no icterus, and results of abdominal ultrasonography were normal. Initial laboratory investigations showed mild leukocytosis (13.45 G/L) and eosinophilia (0.63 G/L), increased

liver enzyme levels (aspartate aminotransferase, 210 U/L; alanine aminotransferase, 211 U/L), and normal bilirubin values. The C-reactive protein level was increased (58 mg/L). Results of 3 blood cultures were negative.

The combination of skin rash, swollen face, liver damage, lymph node enlargement, fever, and documented intake of drugs, which are known elicitors of drug rash with eosinophilia and systemic symptoms (DRESS), or drug-induced hepatitis in the last weeks prompted the suspicion of a severe drug allergy, possibly DRESS. Therefore all drugs were stopped with the exception of prednisolone, doses of which were increased to 40 mg/d. Initially, there was further deterioration, and intravenous methylprednisolone treatment (240 mg/d) was started. This resulted in rapid improvement, which allowed tapering the prednisolone dose to 25 mg over the next 9 days. However, 3 days after reducing the prednisolone dose, in the third week of his disease, lymph node swelling and rash worsened again, and his temperature increased to 40.4°C. The liver enzyme levels peaked at an aspartate aminotransferase level of 1134 U/L and an alanine aminotransferase level of 3440 U/L, eosinophilia increased to 0.87 G/L, and the leukocyte count was 9.9 G/L. Serologic results for hepatitis (types A, B, and C), EBV, cytomegalovirus, HIV, and varicella zoster were negative. Again, intravenous methylprednisolone treatment (240 mg/d) was started. Within a few days, he

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improved clinically (rash), and liver enzyme levels decreased. The corticosteroid treatment could be tapered off within the following 3 weeks.

Six weeks later, while in remission, patch test results (10% in petrolatum) with sulfasalazine, sulfapyridine, 5-aminosalicylic acid, sulfamethoxazole, omeprazole, and diclofenac were negative, but the lymphocyte transformation test (LTT) revealed a

strong proliferation of the patient's lymphocytes to sulfapyridine and sulfamethoxazole (stimulation index, >30; normal value, <2).

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REVIEW

Chemical structure and cross-reactivity in sulfonamide allergy

Sulfonamides are drugs carrying the SO₂-NH₂ group. This chemical entity is present in many different drugs (Table E1). Of allergenic relevance are antibacterial sulfonamides (sulfamethoxazole [SMX], sulfadoxine, and sulfapyridine), which are derivatives of sulfanilamides.^{E1} Sulfanilamides belong to the group of so-called sulfonyl arylamines. Sulfanilamides are characterized by a sulfonamide moiety directly attached to a benzene ring, which carries an unsubstituted amine (–NH₂) at the N4 position (Fig E2, A).

Because immune reactions are directed to the structural component, patients with an allergy to a sulfanilamide might cross-react with other sulfanilamides with a different side chain but not with sulfonamides in general. Laboratory analysis of T-cell reactions and clinical data show that non-sulfanilamide drugs, such as glibenclamide, furosemide, and celecoxib, are not stimulatory and tolerated by patients allergic to sulfanilamides.^{E2-E4} The term “sulfa allergy” is therefore misleading.

Sulfasalazine, which was the relevant component in our patient, is split in the gastrointestinal tract into 5-aminosalicylic acid and sulfapyridine (Fig E2, B). Sulfapyridine is a sulfanilamide. It is not used as an antibacterial but rather as an antirheumatic agent. Importantly, a patient with an SMX allergy should avoid sulfasalazine, and patients who react to sulfasalazine should never again obtain an antibacterial sulfonamide (sulfanilamide).^{E3}

Immunology of sulfanilamide allergies

The mechanism of sulfanilamide hypersensitivity reactions involves IgE, occasionally IgG, and different types of T cell-mediated reactions. The best analyzed drug is SMX contained in cotrimoxazole (together with trimethoprim). SMX is a prodrug: it is metabolized intrahepatically to SMX-NHOH, which is further oxidized to SMX-NO (also in the periphery; Fig E2, C). SMX-NO is highly reactive by binding to cysteines in soluble and cell-bound proteins. It thus can elicit an IgE response, a T cell-mediated response, or both to modified proteins, which can result in different clinical pictures.

Importantly, SMX can also directly stimulate T cells without prior metabolism or binding to a protein. It is a typical example of the pharmacologic interaction with immune receptor (p-i) concept, namely that a drug directly binds to the HLA receptor (p-i HLA), T-cell receptor (p-i TCR), or both and thereby indirectly or directly elicits T-cell stimulation.^{E5}

Clinic of sulfonamide hypersensitivities

Sulfonamides are associated with various side effects, such as nausea, hematopoietic disorders, porphyria, and hypersensitivity reactions. Only some of these side effects are mediated by specific immune responses and can be classified as true allergic reactions. Under treatment with sulfonamide antimicrobial agents, approximately 2% of the general population have adverse drug reactions suggestive of an allergic mechanism.^{E2} True allergic reactions of the anaphylactic type (IgE-mediated urticaria and anaphylaxis) are rather rare, as are IgG antibody-mediated reactions (mainly hemolytic anemia). Rather frequent are T cell-mediated reactions of different severity. Most common are rashes, such as maculopapular exanthemas, but sulfanilamides are also a relevant cause

of serious cell-mediated reactions, such as DRESS, Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN).

A special problem is the rather high occurrence of a sulfanilamide-related side effect in patients with HIV infection. Cotrimoxazole was widely used in prevention and treatment of opportunistic infection in HIV-positive patients. The prevalence of rashes is higher than in the general population.

Two sulfonilamide (amprenavir und fosamprenavir) are used as protease inhibitors in HIV therapy. They induce a high degree of rashes (19% to 29%), which in 1% to 3% of treated persons cause a stop of therapy.^{E6} Desensitization has been described.^{E7} Although neither clinical nor *in vitro* data on immunologic cross-reactivity with other sulfanilamides are available right now, it seems prudent to avoid such drugs if a previous severe allergy to a sulfanilamide in the patient has occurred.

Sulfanilamides and DRESS

Sulfanilamide allergies include potentially life-threatening reactions, such as SJS/TEN and DRESS, which is also called drug (induced) hypersensitivity syndrome (DHS or DiHS), because not all patients have eosinophilia.^{E8} It appears typically after a 2- to 10-week drug exposure. It is clinically characterized by skin rash, fever, lymph node swelling, hepatitis, or involvement of other organs. Many patients have facial swelling; some have signs of a capillary leak syndrome, probably related to the excessively high cytokine values observed during the acute disease. Many patients have activated lymphocytes in the circulation (lymphoblasts), and more than 70% have marked eosinophilia (often >1 G/L). The lethality is 5% to 10% and mainly caused by liver failure. There are some peculiar features that make DRESS a vexing disease.

First, recurrent symptoms long after having stopped drug treatment is common for patients with DRESS. It is often related to reactivation of herpesviruses, in particular human herpesvirus 6, EBV, or cytomegalovirus.^{E9}

Second, also of importance is the intolerance of other drugs/chemicals during the active phase of DRESS: different “innocuous” drugs, such as acetaminophen, can cause clinical exacerbations (flare-up reactions), and this can be observed as long as activated lymphocytes are detectable in the circulation.^{E8} Occasionally, even a permanent second drug allergy to a further compound can develop (ie, multiple drug hypersensitivity syndrome).^{E9}

Diagnosis

Sulfonamide hypersensitivity reactions can be clinically suspected by the constellation of exposure, timing, patterns of organ manifestations, and underlying conditions.

In the acute phase of an anaphylactic reaction, increased serum tryptase levels (1-4 hours after anaphylaxis) support the diagnosis of an acute allergy. However, these tests do not pinpoint the relevant drug. An allergy workup is normally recommended 1 to 6 months after the reaction. It might comprise skin and *in vitro* tests. The sensitivity of these tests is probably low, but the specificity is good, which makes a positive result valuable. Intradermal skin tests might be helpful in both immediate and nonimmediate reactions. SMX at a concentration of 80 mg/mL has been shown to be nonirritating in intradermal tests,^{E10} but the sensitivity of intradermally applied SMX in different skin manifestations is not known. In addition, intradermal skin tests have a small risk for

eliciting systemic allergic reactions (mostly mild and transient). Patch tests and LTTs are used in Europe in patients with nonimmediate reactions. The latter seems to have a fairly good sensitivity and specificity in lamotrigine- and carbamazepine-induced DRESS.^{E11,E12}

The risk of a patch test (10% in dimethyl sulfoxide or petrolatum) is negligible; however, its sensitivity seems to be lower than that of late (24 hours) reading of intradermal tests.^{E13} In our experience the LTT seems to be more sensitive and allows also testing compounds *in vitro*, which are not available for *in vivo* tests. This *in vitro* test measures the drug-induced proliferation of the patient's PBMCs during a 6-day culture.^{E12} However, the LTT and its variants are still rather complex procedures that require skilled personnel and experience with the drug in *in vitro* assays.^{E14}

Treatment

The presumably causative drugs should immediately be withdrawn.

In nonimmediate SMX reactions with mild rashes and no signs of mucosal or extracutaneous symptoms, the cotrimoxazole treatment can be continued or readministered after a "desensitization" protocol. Such "treating through" or "desensitization" is most often used in HIV-positive patients and is successful in 44.4% to 79% of cases.^{E15} It requires monitoring for systemic involvement (fever, eosinophilia, lymphadenopathy, and hepatitis). In most cases an immune-mediated pathomechanism has not been shown.

In patients with severe nonimmediate reactions, such as the index patient, the T-cell immune system is massively activated, and these patients might temporarily react to many "innocuous" drugs with a flare-up. Thus it is our practice to reduce drug therapy in patients with DRESS as much as possible as long as activated lymphocytes are detectable in the circulation.

For the treatment of DRESS with severe organ involvements (eg, alanine aminotransferase/aspartate aminotransferase level >500 U/L), corticosteroids are often used. Patients with sulfanilamide-induced SJS/TEN should be handled like other patients with SJS/TEN and are best referred in specialized (eg, burn) centers experienced in the care of such patients.

The case revisited

The clinical course of this patient shows typical symptoms of DRESS: skin rash, fever, lymph node enlargement, hepatic involvement, and eosinophilia. The sulfanilamide-containing drug sulfasalazine was suspected as the causative drug, although omeprazole/esomeprazole or diclofenac can also induce liver damage. Even though the drugs were stopped, there was a worsening after initial improvement, which is not uncommon in

patients with DRESS and is usually related to reactivation of herpes viruses (human herpesvirus 6, EBV, or cytomegalovirus). However, we did not detect an increase in antibody levels (viral loads were not determined). It is also possible that a too rapid tapering of corticosteroids might have caused the transient relapse.

An allergy workup revealed a strong *in vitro* reaction (LTT) to sulfapyridine and the cross-reactive SMX. Results with the other drugs were all negative.

The diagnosis of sulfapyridine (sulfasalazine)-induced DRESS was made: the patient was informed carefully about his severe drug allergy and advised to strictly avoid all sulfanilamides. This warning of the use of antibacterial sulfonamides was also included in his "allergy passport."

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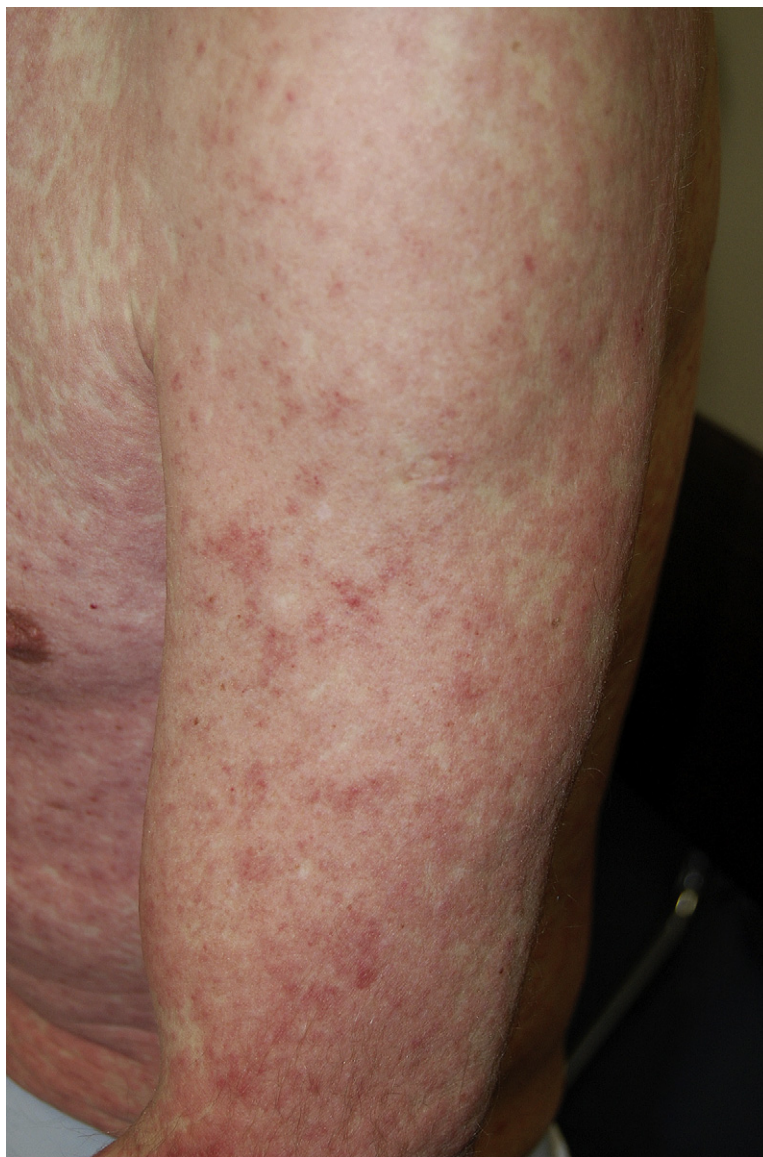


FIG E1. Erythematous exanthema 3 weeks after the start of treatment with oral diclofenac, omeprazole, and sulfasalazine.

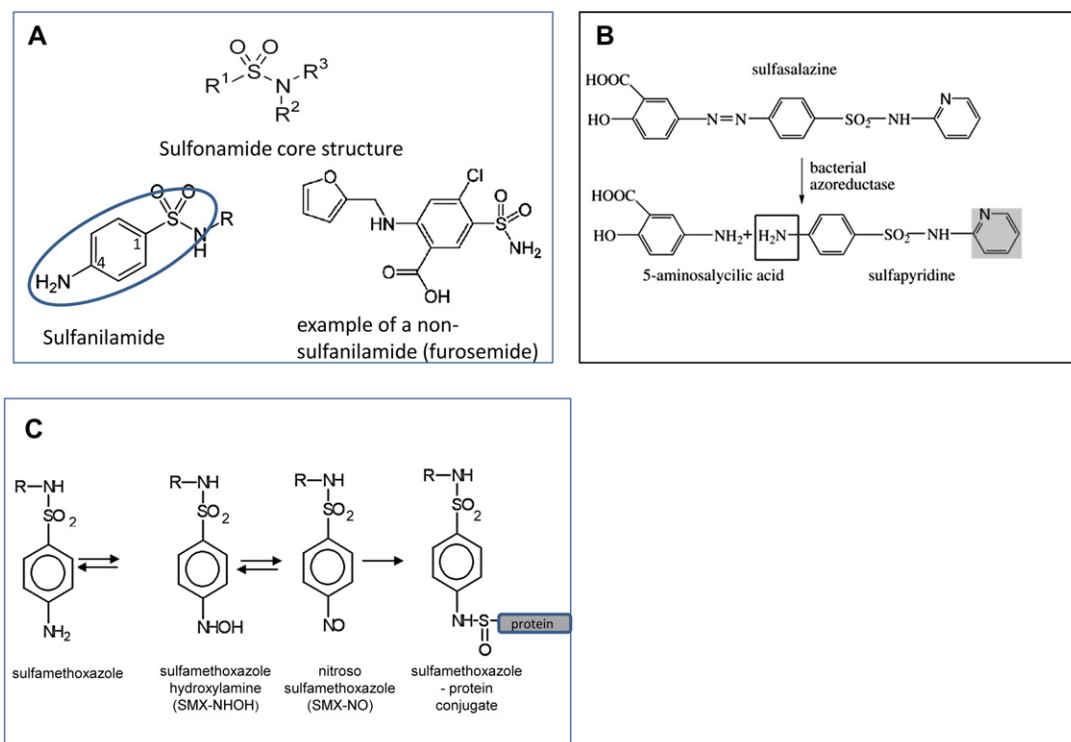


FIG E2. **A**, The sulfonamide core structure contains a sulfonyl group connected to an amine group. Sulfonamide antibiotics are sulfanilamides, in which a sulfonamide is attached to a benzene ring with an unsubstituted amine ($-\text{NH}_2$) moiety at the fourth position. Many other sulfonamide drugs might also contain a benzene ring but are non-sulfanilamides (eg, furosemide). For more information, see [Table E1](#). **B**, Sulfasalazine is split by bacterial enzymes in the colon in 5-aminosalicylic acid and sulfapyridine, which is a sulfanilamide. **C**, SMX is metabolized intrahepatically to SMX-NHOH, which is further oxidized to SMX-NO; the later binds covalently to cysteines in proteins.

TABLE E1. Classification of sulfonamides

Sulfanilamides (sometimes referred to as sulfonyl-arylamines)	Non-sulfanilamides
Antibacterial agents:	COX-2 inhibitors:
Sulfadiazine	Celecoxib
Sulfamethoxazole	Etoricoxib
Sulfisoxazole	
Sulfapyridine (in sulfasalazine)	
Protease inhibitors:	Carbonic anhydrase inhibitors:
Amprenavir	Acetazolamide
Fosamprenavir	Brinzolamide
	Dorzolamide
	Methazolamide
	Diuretics:
	Bumetanide
	Chlorthalidone
	Chlorothiazide
	Diazoxide
	Furosemide
	Hydrochlorothiazide
	Indapamide
	Metolazone
	Torsemide
	Sulfonylureas:
	Chlorpropamide
	Glibenclamide
	Glimepiride
	Glipizide
	Glyburide
	Tolbutamide
	Tolazamide
	Others:
	Ibutilide
	Sotalol
	Topiramate
	Zonisamide